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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,468	01/04/2001	Patrick L. Iversen	0450-0033.30	3548

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 10/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/754,468	Iversen et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 1, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-6, 13, 14, 17, 19-23, 30, 31, and 34-41* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-6, 13, 14, 17, 19-23, 30, 31, and 34-41* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *9, 10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed August 1, 2002, Paper No. 13.

Election/Restriction

Applicant's election with traverse of the target E. coli secA protein in Paper No.13 is acknowledged. The traversal is on the ground(s) that in most cases up to 10 independent and distinct nucleotide sequences have been examined in a single application without restriction and that nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions. This is not found persuasive because the expanding data bases that must be searched in determining the patentability of each nucleotide sequence have significantly increased the search burden and consequently each sequence is treated as a separate invention.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that Applicant timely traversed the restriction (election) requirement in Paper No. 13, as well as canceling the non-elected claims. Remaining claims 1, 3-6, 13, 14, 17, 19-23, 30, 31, 34-41 have been examined on the merits as indicated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-6, 13, 14, 17, 19-23, 30, 31, 34-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 3-6, 13, 14, 17, 19-23, 30, 31, 34-41, the phrase "effective to hybridize to a target sequence" is vague and unclear (i.e. effective to specifically hybridize to the sec-A target sequence and inhibit expression?). Clarification is requested.

In claim 1, lines 5-6, it is unclear what the phrase "containing a translational start codon" is referring to (i.e. Does it refer to the antisense oligonucleotide or the target gene?).

In claim 17, lines 6-7, it is unclear what the phrase "containing a translational start codon" is referring to (i.e. Does it refer to the antisense oligonucleotide or the target gene?).

In claim 36, lines 7-8, it is unclear what the phrase "containing a translational start codon" is referring to (i.e. Does it refer to the antisense oligonucleotide or the target gene?).

Claims 4, 5, 20, 21, 22 and 40 refer to figures in the specification and should be written in a form that is independent of the need to refer to figures, if possible.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 19-23, 30, 31, 34-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of E. Coli growth

comprising the administration of antisense, does not reasonably provide enablement for methods of treating or preventing any and/or all bacterial infections in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for treating any bacterial infection in an organism comprising the administration of morpholino based antisense oligonucleotides which specifically target and inhibit the expression of E. Coli sec-A. The claims are also drawn to methods of vaccinating an organism against E. Coli comprising the administration of replication crippled, morphologically abnormal E. Coli cells prepared by incubating the E. Coli in the presence of a morpholino based antisense which specifically targets and inhibits the expression of E. Coli sec-A protein.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in

treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the

current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

Zollinger et al teach the unpredictability of developing vaccines, pointing to problems in identifying active components among the heterogenous array of molecules provided by bacteria which are to be utilized in generating successful vaccines, as well as problems in predicting the duration of protection for a given potential vaccine (See entire document, especially pages 37-38 and 42). Gilbert et al also teach the difficulties in vaccine development, attributed to many factors including a lack of systematic quantitative investigation in the differences in antigenically diverse infectious pathogens, as well as a general lack of systematic categorization of pathogen variation, including differences between pathogen genotypes and vaccine preparation for a particular pathogen (see entire document, especially pages 68-69, 71, 81-83, figure 1 on page 70 and table 3 on page 80).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting or treating any bacterial infections in an organism comprising the administration of antisense, nor has any guidance been provided for preventing any disease or condition associated with bacterial infections in an organism.

The specification teaches the inhibition of E. Coli growth in culture following administration of morpholino based antisense which specifically target and inhibit the expression of E. Coli sec-A protein. The specification fails to teach the treatment or prevention of any bacterial infection in an organism comprising the administration of antisense oligonucleotides or comprising the administration of replication crippled bacteria. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of bacterial growth as being correlative or representative of the successful treatment of bacterial infection in an organism, nor of being correlative or representative of the successful vaccination of an organism for protection from E. Coli infection comprising the administration of replication crippled bacteria in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of antisense in treating an organism for any and/or all bacterial infections comprising the administration of antisense which target E. Coli sec-A or with predetermining the efficacy of a vaccine comprising replication crippled E. Coli. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed, which treatment methods are for any bacterial infection in an organism, as well as the known unpredictability of vaccine efficacy for a pathogen infection in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for

treating any bacterial infection in an organism comprising the administration of morpholino based antisense oligonucleotides which specifically target and inhibit the expression of E. Coli sec-A. The claims are also drawn to methods of vaccinating an organism against E. Coli comprising the administration of replication crippled, morphologically abnormal E. Coli cells prepared by incubating the E. Coli in the presence of a morpholino based antisense which specifically targets and inhibits the expression of E. Coli sec-A protein. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring bacteria in an organism whereby sec-A expression is inhibited in vivo, and further that treatment effects are provided for any and/or all bacterial infections, or whereby E. Coli infection is prevented in an organism comprising the administration of replication crippled bacteria generated by administration of antisense targeting and inhibiting expression of sec-A protein in the bacteria, prior to their administration to the organism. Since the specification fails to provide any particular guidance for the inhibition, prevention or treatment of any bacterial infection in any organism comprising the administration of antisense or replication crippled bacteria, and since determination of these factors, including predicting vaccine efficacy, is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6, 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zyskind et al in view of the combination of Cook and Arnold, Jr. et al.

The claims are drawn to antibacterial compounds consisting of antisense oligomers between 10 and 20 bases in length, which oligonucleotides comprise a targeting sequence effective to hybridize to a nucleic acid sequence encoding E. Coli sec-A, and which oligonucleotides are substantially uncharged, wherein adjacent subunits within each oligonucleotide are joined by uncharged (e.g. phosphor(di)amidate, carbonate, carbamate, amide linkages), or comprising charged phosphoramidate, phosphate or phosphorothioate linkages, which ratio of uncharged to charged linkages in the oligomers is at least 4:1.

Zyskind et al teach antisense oligonucleotides comprising phosphorothioate internucleotide linkages, which oligonucleotides are effective to hybridize and inhibit the expression of a nucleic acid molecule encoding E. Coli sec-A (See especially figure 11, col. 8, line 23-col. 9, line 40; col. 13, line 1- col. 18, line 30; and accompanying sequence alignment data).

Zyskind et al do not teach a minimum ratio of uncharged to charged linkages within the oligonucleotide of 4:1.

Arnold, Jr. et al teach relationship between incorporating various ratios of uncharged to charged linkages and antisense target binding, Rnase activation, antisense stability and cellular uptake (penetration), which charged groups include phosphodiesters and phosphorothioates and which uncharged groups include aryl- and alkyl-phosphonates, phosphoramidates and phosphotriesters, as well as alkyl- and aryl-phosphonothioates (see especially col. 2, line 42-col. 4, line 6).

Cook et al teach the significance and distinguishing features of various internucleotide linkages (e.g. involving phosphorothioates, methylphosphates, phosphotriesters, phosphoramidates and phosphodiesters), which features includes solubility characteristics imparted to the oligonucleotides, nuclease resistance, Rnase activating abilities, facilitating cellular uptake and cellular penetration (See especially col. 1, line 36-col. 2, line 14; claims 1-8).

It would have been obvious to one of ordinary skill in the art to utilize antisense oligonucleotides which target and inhibit the expression of E. Coli sec-A, because the polynucleotide sequence of E. Coli sec-A and the utilization of antisense which target and inhibit the expression of sec-A as an antibacterial agent had been taught previously by Zyskind et al. It would have been obvious to one of ordinary skill in the art to incorporate mixed internucleotides linkages, including uncharged and charged linkages, because such mixed linkages had been incorporated into antisense oligonucleotides previously by both Arnold and Cook because a

combination of charged and uncharged linkages impart a combination of useful properties for antisense oligonucleotides such as enhanced target binding, stability from nuclease degradation, Rnase activation and cellular uptake, which properties have been exploited previously by Zyskind et al, Arnold and Cook. One of ordinary skill in the art would have been motivated to design antisense oligonucleotides comprising both charged and uncharged oligonucleotides in order to enhance stability, modulate solubility, enhance cellular uptake, target binding and Rnase activation. One of ordinary skill in the art would have expected that a ratio within the range of 3-5:1, uncharged to charged linkages would be suitable for enhancing target binding and cellular uptake, because such a range was utilized by Arnold (e.g. see figure 7 and col. 3, line 62-col. 4, line 6 of Arnold).

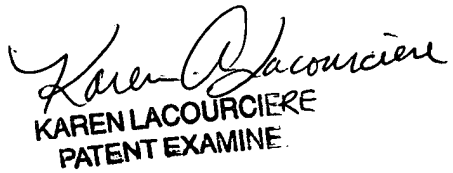
Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be

retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



JZ

October 19, 2002